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Leiomyosarcoma of the Inferior Vena Cava: A Clinicopathologic Review and Report of Three Cases

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Background and Objectives: We operated on three patients with leiomyosarcoma of the inferior vena cava.
Methods: Complete excision was possible in all three patients.
Results: One patient developed widespread metastasis at 23 months, one patient is alive with no evidence of disease at 70 months, and one patient is alive at 15 months. The third patient had subcutaneous and pulmonary metastases at the time of presentation, which are radiologically nondetectable at present following postoperative chemotherapy.
Conclusions: The clinicopathologic features, prognostic factors, and treatment of 130 cases found in a comprehensive literature search and our three cases are reported. *J. Surg. Oncol. 1997;65:205–217.* © 1997 Wiley-Liss, Inc.

KEY WORDS: leiomyosarcoma; inferior vena cava

INTRODUCTION

Leiomyosarcoma (LMS) of the inferior vena cava (IVC) is a rare tumor, with <200 cases reported in the world literature. The great majority of cases reported to date are single case reports or small series of cases. The clinicopathologic features, prognostic factors, and the management of this tumor have not been adequately described.

In this report we present our three cases. The clinicopathologic features, prognostic factors, and treatment and outcome of 130 cases collected from the literature are reviewed in addition.

CASE REPORTS

Case 1

A 73-year-old white female presented with a 1-year history of right flank pain and a 10-pound weight loss. The physical examination was significant for lower extremity edema. A computerized tomography (CT scan) revealed a large heterogenous mass anterior to the right kidney and adjacent to the IVC. The histology of a percutaneously obtained biopsy was consistent with a low grade leiomyosarcoma. At celiotomy, a well-circumscribed tumor originating from the IVC above the right renal vein was found. The tumor was excised en bloc with the right kidney, right adrenal gland, and a cuff of IVC wall. The defect in the vena cava was closed primarily, thus maintaining the patency of the vein. The patient did well for 23 months only to be readmitted with bowel obstruction. A CT scan revealed multiple lung metastases and no intra-abdominal tumor. At celiotomy, a tumor mass was identified in the lesser omentum, and biopsy was consistent with LMS. Postoperatively, the patient developed acute pancreatitis progressing to multiple system organ failure and death. At autopsy, there was acute pancreatitis, locally recurrent and metastatic LMS in the peri-aortic lymph nodes, liver, pancreas, and both lungs. Pathologically, the primary tumor was an extraluminal LMS arising from the media of the vein, measuring 11 × 9 × 9 cm, and exhibiting 1–5 mitoses per high power field.

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Case 2

A 48-year-old female presented with vague right flank pain of several months duration. A CT scan of the abdomen revealed a large retroperitoneal tumor to the right side of the midline. At surgery a large tumor involving the hilum of the right kidney was identified. En bloc resection to include the tumor, right kidney, adrenal gland, and a segment of the IVC was performed. The cut ends of the IVC were oversewn with preservation of the continuity of the left renal vein with the upper stump of the IVC. The patient remains alive and well with no evidence of lower extremity edema 70 months after surgery. Pathologically, the primary tumor was a grade I–II LMS arising from the media of the IVC, growing extraluminally and measuring 11 cm.

Case 3

A 77-year-old white male presented with right thigh and arm subcutaneous nodules. The histology of excisional biopsies was consistent with LMS. A CT scan of the chest, abdomen, and pelvis revealed multiple pulmonary nodules and a large retroperitoneal tumor. At surgery a tumor arising from the anterior wall of the IVC below the renal veins was identified. Resection of the tumor with a portion of the IVC wall was performed. The resultant defect in the IVC was closed primarily, thus preserving the continuity of the vessel. Postoperatively, Dacarbazine (DTIC) 300 mg/m^2 and Ifosfamide 2,500 mg/m^2 as a continuous intravenous infusion (I.V.) was given daily for 3 days, repeated every 4 weeks, for six courses with initial radiologic regression, then stabilization of pulmonary metastases. Subsequently, Cisplatinum 80 mg/m^2 I.V. repeated every 4 weeks was initiated. The pulmonary metastases are visible only on CT scan. The patient remains alive and with no symptoms at 15 months. Pathologically, the tumor was a grade I, extraluminal LMS of the IVC.

DISCUSSION

Leiomyosarcoma accounts for 7% of soft tissue sarcomas [1]. Three groups of LMS are identified: cutaneous and subcutaneous, retroperitoneal and intra-abdominal, and LMS of vascular origin. LMS of vascular origin is rare with less than two tumors found in 14,000–34,000 autopsies [2–4]. These tumors are five times more common in the venous system, and >50% occur in the inferior vena cava (IVC) [5–12]. Since Perl's first description of a LMS of the IVC in 1871 [13], <200 cases have been reported in the literature, the great majority being single case reports. The largest series from one institution was reported by Burke and Virmanti in 1993 [12]. They described 15 cases retrieved from the Data Division of the Armed Forces Institute of Pathology in a search involving the period 1976 through 1991.

In a comprehensive review of the literature, we collected 130 cases and added our own three cases in an attempt to identify the salient features of this unusual tumor. The clinicopathologic features and outcome of treatment of a total of 132 cases are depicted in Tables I and II. One case is not included in either table, since the treatment modality is not specified [14].

Pathologic Features

LMS of the IVC is a mesenchymal tumor that originates from the media of this vein. In the early stages it remains confined to the wall of the vein as a mural growth. As it grows in size, the tumor expands extraluminally (extrinsic growth), intraluminally (intrinsic growth), or in a bidirectional fashion as a dumbbell growth. The site of origin of the tumor from the cava is described in relation to the hepatic and renal veins. For this purpose the IVC is divided into three portions: upper portion (Level 1), extending from the entry of the hepatic veins up to the right atrium; middle portion (Level 2), extending from the renal veins to the hepatic veins; and lower portion (Level 3), extending from the confluence of the iliac veins to the entry of the renal veins.

Pattern of growth. Mural growths occurred in 9 cases (6.8%), extraluminal in 39 cases (29.3%), intraluminal in 32 cases (24%), and dumbbell in 37 cases (27.8%). The pattern of growth was not specified in 16 cases (12%). The intrinsic growth had a tendency to extend intraluminally as a propagating tumor thrombus. This occurred in 43 cases (33%). The tumor thrombus was limited in extent in 4 cases (9%), and it was more extensive in 39 cases (91%). The tumor thrombus extended into the hepatic veins in 18 cases, right atrium in 22 cases, right ventricle in 1 case, and into the pulmonary artery or its branches in 2 cases.

Site of origin. The tumor originated from Level 1 in 6 cases (4.5%), Level 2 in 36 cases (27%), and Level 3 in 37 cases (27.8%). The level of origin was not specified in 12 cases (9%). We found that in 42 cases (31.5%) the tumor could not be assigned to one level of the IVC. Such tumors were classified as Level 1,2 or Level 2,3, and even Level 1,2,3 (LMS of the entire IVC) [9,15]. Some of these tumors originated in the area of the hepatic or renal veins and hence were considered bilevel tumors (Level 1,2 or Level 2,3). For other tumors, particularly those with intracaval growth, the upper and lower limits of the growth, rather than the origin of the tumor, were described. We did not find any indication that such tumors were multicentric or diffuse in nature. We classified these tumors as ''site of origin not specified,'' and hence none of the tumors reviewed by us were considered ''LMS of the entire IVC.''

Gross pathology. LMS of the IVC originated from a localized area of the cava wall, thus forming the base of the tumor that measured 2 cm to 5.5 cm [10,16–22]. It was sessile and in only two cases the tumor possessed a stalk (1.5%) [16,22].

The extraluminal growth assumed a globular shape and appeared bosselated and encapsulated. The capsule was composed of compressed surrounding tissue acquired as the tumor grew in size. The intraluminal growth appeared as fine or coarse nodulations on the intimal surface of the IVC. As it extended intacavally as a propagating tumor thrombus, the intrinsic growth acquired the configuration of the IVC, i.e., oblong shape. The tumor had a tendency to remain confined to its capsule and the overlying adventitia remained intact. Such confines were violated in seven cases (5.3%) [16,17,23–26]. In some cases the liver was described as being ''infiltrated by tumor in the region of the hepatic veins.'' This phenomenon represented intravenous extension, i.e., a propagating thrombus into the hepatic veins [27–33]. However, the continuity of the overlying intima was often interrupted.

On cut section, the tumor appeared yellow-white, pinkish-gray, or tan-white in color with lobular architecture. Areas of hemorrhagic necrosis and cystic degeneration were frequently present. The weight of the tumor ranged from 60 gm to 3,500 gm and the size ranged from 1.5 cm to 30 cm. The dimensions varied according to the configuration of the tumor.

Histology. LMS of the IVC exhibited a typical pattern of interlacing sweeping bundles of spindle-shaped cells with elongated, blunt-ended nuclei with a tendency to palisade. The microscopic picture varied from a benign appearance with monotonous, cellular uniformity and little mitotic activity to a highly malignant one with hyperchromatism, hypercellularity, bizarre-shaped nuclei, and numerous mitoses. Mitotic figures varied within the same tumor. The tumor was poorly differentiated, grade III, or exhibited mitotic figures more than 10/hpf in 18 of the 46 cases (39%) in which such data were specified. Mononuclear giant cells were present to a variable degree, and areas of necrosis were commonly seen. Masson's trichrome and Van Gieson's stain indicated the presence of collagenous tissue. Immunohistochemical and ultrastructural studies were scarce, but would be expected to reflect features found in soft tissue sarcoma of other sites. Tumor cells displayed desmin, vimentin, and smooth muscle actin, but not S-100 protein [12,28,34]. A high desmin immunoreactivity rate exceeding that seen in other soft tissue LMS was noted [12]. Myofibrils, intracytoplasmic actin-type filaments, peripheral cytoplasmic micropinocytotic vesicles, and occasional tight junctions between tumor cells were described [28,35,36].

Clinical Presentation

Females were affected in 75–80% of the cases, with a white-to-black ratio of 5 to 1. The patients' ages ranged from 24 to 83 years, with a mean of 58 years.

The diagnosis of LMS of the IVC was often delayed. Despite its large size, the tumor remained asymptomatic for a long time. The presenting symptoms were nonspecific and varied. Because of its rarity, the tumor was not suspected as the culprit in the genesis of the symptomatology in the majority of cases. The tumor was not appreciated on physical examination in two-thirds of the cases and was missed occasionally at laparotomy performed for other unrelated conditions, although it was of appreciable size [3,31,37]. In one-third of the cases, the tumor was diagnosed only at autopsy, in patients who were symptomatic. Its deep-seated location, the presence of the liver and ascites, and the absence of an extraluminal growth made its detection difficult. The diagnosis of LMS of the IVC was made or suspected at the time of presentation or prior to surgery in <5% of the patients [34,38–42]. In 28 cases (21%), the patient had been previously operated or simultaneously with the discovery of the LMS, most commonly for uterine myoma [Tables I,II]. There seemed to be an association among female gender, LMS of the vein, and multiple endocrine morphological changes [33].

The tumor was asymptomatic in 14 cases (10.5%) [3,7,8,12,24,31,35,37,43–48]. It was found on routine physical examination, at celiotomy performed for other unrelated conditions, or as an incidental autopsy finding in patients who died from other disease process. Pain was the most common complaint experienced by one-half of the patients. It was associated with tumors arising from any level of the IVC. Weight loss, nausea, and or vomiting occurred in one-fourth of cases. One-fifth of the patients reported fever and weakness.

Interference with the circulation on the right side of the heart by the tumor or tumor thrombus resulted in a host of manifestations. Patients presented with clinical picture of constrictive pericarditis, cardiac valvular, hepatic, renal, or pulmonary disease, idiopathic IVC thrombosis, deep vein thrombosis, or pulmonary embolism [2,3,9, 12,13,19–21,23,29,33,39,49–55]. Budd-Chiari syndrome (BCS) (hepatomegaly, ascites, anasarca, hepatic failure and coma) developed in one-fourth of the cases. It occurred when the ostia of the hepatic veins were occluded by tumors arising in the area of the hepatic veins, or when propagating tumor thrombi extended into the lumen of the hepatic veins. Extension of the tumor thrombus into the right atrium resulted in tricuspid valve obstruction in one (0.7%) [51]. Further extension into the pulmonary artery or its branches resulted in manifestations of pulmonary embolism in two cases (1.5%) [19, 20]. Gastrointestinal hemorrhage occurred in three cases (2.3%) [21,49,52]. The source of bleeding in one case was not identified, was variceal in origin in the second, and the result of direct invasion of the duodenum by tumor in the third [21,49,52]. Compression of the renal artery by tumor resulted in renovascular hypertension in one case (0.75%) [56]. A mass was palpable in one-third of the cases, the great majority of which were intrahepatic in origin.

TABLE I. Leiomyosarcoma of the Inferior Vena Cava, Nonresected Cases (N = 43): Pathologic Features and Cause of Death

Ref.	Level[a]	Growth pattern[b]	Size (cm)	Mitosis grade[c]	Associated pathology	Extent of tumor[d]	Cause of death[e]
[2]	1,2	Intr.	10 × 5 × 5	Low	—	Tumor thrombus into HV	BCS
[3]	1	Dumbbell	E:7 × 7 × 3.5 I:21 × 9 × 6	Well diff	Uterine myoma, goitre	Tumor thrombus into RA and down to RV; liver metastases	BCS
[3]	3	Dumbbell	E:13 × 10 × 9	Well diff	Rectal cancer, goitre, meningioma	Tumor filling IVC	Sepsis, S/P enterolysis
[6]	NS	Extr.	4	7–20/10 hpf	—	—	Uremia
[7]	2	Mural	2.5 × 1.5	1/6 hpf	Goitre	—	Myxedema
[8]	3	Dumbbell	4	Common	—	—	Uremia
[11]	NS	NS	Large	—	—	—	Hemorrhage
[12]	3	Mural	—	—	—	Metastatic disease at time of presentation	NS
[12]	NS	Intr	—	—	—	Tumor thrombus from RA to iliac veins	IV syndrome
[13]	1,2	Intr	10	—	—	Tumor thrombus to level of RV and liver; lymph node metastases	BCS
[17]	1,2	Dumbbell	11 × 11 × 6	—	—	Tumor invading aorta	BCS
[19]	1,2	Intr	3.5	Scarce	Uterine myoma	Tumor thrombus into thigh veins, and terminal branches of pulmonary artery; renal metastases	Tumor pulmonary embolism
[20]	3	Intr	—	Numerous	—	Tumor thrombus to pulmonary artery and tumor fragments in its terminal branches	Tumor pulmonary embolism
[21]	NS	Intr	3	—	—	Tumor filling IVC from diaphragm to branching of iliac veins, lymph nodes and liver metastases	Variceal hemorrhage, BCS
[23]	1,2	Dumbbell	13 × 7 × 7	Mixed	—	Tumor from RV to RA, thrombus into HV and RA; lung metastases	BCS
[27]	3	Intr	Large	—	Uterine myoma, benign breast disease	Tumor thrombus into RA, HV, and outside HV into liver parenchyma	BCS
[28]	1,2	Intr	7 × 6.5	2/10 hpf	—	Tumor occupying upper two thirds of IVC; tumor thrombus to RA	BCS, DIC
[29]	2	Dumbbell	E:6	—	—	Tumor thrombus into RV, RA, HV	BCS
[30]	NS	NS	Large	—	—	Tumor extended into RA, HV, and to level of RV	BCS
[30]	NS	NS	—	—	—	Tumor infiltrated liver in region of HV; lung and renal metastases	NS
[31]	1,2	Intr	17 × 9 × 9	—	Multiple myomata in gastroesophageal junction	Both lobes of liver infiltrated in the region of HV; lung and renal metastases	BCS, pneumonia
[32]	NS	Intr	—	—	—	—	BCS
[33]	NS	Intr	16 × 6 × 6.5	Well diff	Chromophobe adenoma, nodular adrenal hyperplasia, adundant islands of Langerhans, proliferative ovarian theca cells	Tumor extending from above RV into RA; tumor thrombus into HV; lung metastases	NS
[34]	22	Intr	4.5	—	—	Tumor thrombus into RA and HV	BCS

Continued

TABLE I. Leiomyosarcoma of the Inferior Vena Cava, Nonresected Cases (N = 43): Pathologic Features and Cause of Death (Continued)

Ref	Level[a]	Growth pattern[b]	Size (cm)	Mitosis grade[c]	Associated pathology	Extent of tumor[d]	Cause of death[e]
[36]	2	Intr	—	Several	Uterine myoma	—	Sepsis
[38]	2	Dumbbell	E:5 I:10	Few	Uterine lesion, NS	Radiotherapy; tumor thrombus to level of diaphragm and into HV	Alive at 8 weeks
[42]	NS	Intr	—	—	—	Tumor from RV to RA; tumor thrombus into HV; lymph node metastases	
[49]	1	Intr	Large	—	Uterine myoma, lung cancer, benign breast tumor	Tumor thrombus to level of tricuspid valve	Variceal hemorrhage, BCS
[50]	NS	Intr	—	Poorly diff	Uterine myoma, breast cancer.	Tumor filling IVC and its tributaries; Liver metastases	BCS
[51]	1	Dumbbell	E:10 × 10 × 6	Poorly diff	Uterine myoma	Tumor thrombus into right ventricle and HV; bone metastases	Tricuspid valve obstruction
[53]	1,2	Dumbbell	16 × 16 × 3	—	Uterine myoma	Tumor thrombus into RA	BCS
[54]	1,2	Intr	9 × 7 × 4	Occasional	Uterine myoma, goitre	—	BCS, PE
[55]	NS	Intr	—	—	Uterine myoma	Tumor filled IVC from above RV; tumor thrombus into RA, HV, hepatic sinusoids, and liver parenchyma; liver metastases	BCS
[57]	NS	Dumbbell	E:11x8x4 I:26 × 5	40/50 hpf	—	Tumor filling IVC; tumor thrombus into RA and IVC tributaries; liver and lung metastases	BCS
[59]	NS	Intr	4 × 4 × 5	Multiple	Renal angiolipoma, adenoma, hemangioma. Hepatic adenoma, hemangioma. Islet cell tumor, nesidioblastosis. Alveolar hyperplasia	Tumor filling upper 4/5th of IVC; tumor thrombus into HV, RA, and RV	BCS, pneumonia
[60]	1,2	Dumbbell	—	2	—	Tumor thrombus into RA; tumor into right lobe of liver	BCS, shock
[77]	NS	NS	—	—	—	Tumor from RV to above HV	BCS
[80]	NS	Dumbbell	19 × 10 × 6	Not common	—	Tumor from above HV to below RV	BCS
[87]	1,2	Intr	4	—	—	—	BCS
[90]	1,2	Intr	17.5 × 5 × 2	—	—	Tumor thrombus filling IVC	BCS
[91]	2	Dumbbell	Huge	Low	—	Limited tumor thrombus to level of liver	BCS
[92]	NS	Intr.	6	—	—	Tumor thrombus into RA, HV, and iliac veins	BCS
[94]	1	Intr.	—	—	—	Tumor thrombus into RA; Liver and lung metastases	BCS

[a]1: IVC from HV to RA; 2: IVC from RV to HV; 3: IVC from RV to confluence.
[b]Intr = intrinsic; Extr = extrinsic.
[c]Diff = differentiated; hpf = high power field.
[d]HV = hepatic vein; RA = right atrium; RV = renal vein.
[e]BCS = Budd-Chiari syndrome; DIC = disseminated intravascular coagulation; PE = pulmonary embolism; NS = not specified.

TABLE II. Leiomyosarcoma of the Inferior Vena Cava, Resected Cases (N = 89): Pathologic Features, Treatment, and Outcome

Ref	Level[a]	Growth pattern[b]	Size (cm)	Mitosis grade[c]	Associated pathology	Extent of tumor[d]	Further treatment/outcome[e]
[5]	3	Extr	8 × 8 × 5	Numerous	—	—	NED at 3 mo
[9]	3	Extr	11 × 9.5 × 8	Frequent	—	—	Postoperative radiotherapy; lung metastases at 14 mo, chemotherapy; died at 36 mo
[10]	3	Extr	8 × 7 × 4	>35/10 hpf	—	—	Lung metastases at 9 mo, resected; died at 45 mo with liver and lung metastases
[11]	(!)	—	—	—	—	—	Partial excision, regrowth, resected; died at 5 y
[11]	(!)	—	—	—	—	—	Lung metastases, died at 2 y
[11]	(!)	—	—	—	—	—	Died at 3 mo; stroke, pneumonia
[11]	(!)	—	—	—	—	—	Liver metastases; died at 3.5 y
[11]	(!)	—	—	—	—	—	Widespread metastases; died at 7 y
[11]	(!)	—	—	—	—	—	Alive at 7.5 y
[11]	(!)	—	—	—	—	—	Local recurrence, resected; NED at 3 y
[11]	(!)	—	—	—	—	—	Alive at 6 mo
[12]	1	Intr	—	—	—	Tumor thrombus into RA	Died 3 weeks postoperatively
[12]	3	Dumbbell	—	—	—	—	Alive at 16 mo
[12]	3	Mural	—	—	—	—	Lost to follow-up
[12]	2	Mural	—	—	—	—	Postoperative radiotherapy; lung and renal metastases at 36 mo; died at 39 mo
[12]	3	Mural	—	—	—	—	Chest wall and pleural metastases; died at 99 mo
[12]	3	Mural	—	—	—	—	Postoperative chemotherapy; alive at 50 mo
[12]	3	Mural	—	—	—	—	Lost to follow-up
[12]	2	Mural	—	—	—	—	Liver and lung metastases; died at 46 mo
[12]	2,3	Mural intr	—	—	—	—	Postoperative radiotherapy; no follow-up
[12]	2	Dumbbell	—	—	—	—	Postoperative chemotherapy; lung and liver metastases; died at 29 mo
[12]	2	Mural	—	—	—	—	Postoperative chemotherapy; lung and liver metastases; died at 74 mo
[12]	1	Mural intr	—	—	—	Tumor thrombus into RA	Died at 2 mo; Budd-Chiari syndrome
[12]	NS	Mural intr	—	—	—	—	Postoperative chemotherapy; liver metastases; died at 30 mo
[15]	2	Extr	23 × 21 × 14	5–6/hpf	Goitre	—	NED for several years; cardiac death
[16]	2	Extr	20 × 10 × 10	3-high	—	Capsule breached	Local recurrence at 5 mo; gastrojejunostomy + radiotherapy; alive at 3 y.
[18]	3	Extr	30 × 20 × 20	Few	Uterine myoma	—	NED at 2 mo
[22]	2	Dumbbell	16 × 15 × 11	Well diff	Breast cancer	—	NED at 1 y
[24]	3	Extr	—	3	—	Aorta and muscle invaded	Preoperative chemotherapy and radiotherapy; local recurrence at 17 mo, debulking; died from recurrence at 23 mo
[24]	2	Extr	—	15 hpf	—	Liver capsule invaded	Liver met at 7 mo, chemotherapy; died at 2 y
[24]	2	Extr	—	High	Multiple myeloma	—	Preoperative chemotherapy; died at 3 y, unrelated condition
[24]	3	Extr	8	Up to 15 hpf	—	—	Preoperative chemotherapy; intra-abdominal recurrence at 30 mo, chemotherapy + debulking; died at 6 y

Continued

TABLE II. Leiomyosarcoma of the Inferior Vena Cava, Resected Cases (N = 89): Pathologic Features, Treatment, and Outcome (Continued)

Ref	Level[a]	Growth pattern[b]	Size (cm)	Mitosis grade[c]	Associated pathology	Extent of tumor[d]	Further treatment/outcome[e]
[25]	3	Dumbbell	15	—	—	Stomach invaded	Liver and lung metastases at 5 y; resected + chemotherapy and radiotherapy; died at 5 y
[26]	3	Extr	4 × 5 × 5	Well diff	—	—	NED at 78 mo
[26]	3	Dumbbell	10 × 9 × 7.5	Poorly diff	—	Intervertebral spaces invaded	Postoperative chemotherapy and radiotherapy; died at 6 mo, liver and lung metastases
[26]	3	Intr	6.5	Poorly diff	—	—	NED at 20 mo
[29]	2	Extr	Large	—	—	—	No follow-up
[35]	3	Intr	4.5	2/hpf	—	—	NED at 24 mo
[37]	2,3	Dumbbell	E:17 × 15 I:3 × 2.5	Few	Colon polyp, uterine myoma, basal carcinoma	Omental deposit	Alive at 3 y
[39]	2	Extr	—	—	—	—	NED at 10 mo
[39]	2	Extr	Plum size	Poorly diff	—	—	NED at 14 mo
[39]	2	Extr	NS	Poorly diff	—	—	NED at 10 mo
[40]	2	Dumbbell	15 × 6 × 5	High	—	Tumor thrombus into RA	NED at 1 y
[41]	2	Intr	NS	7–10/hpf	—	Portal LN met, tumor thrombus into RA	Partial excision + radiotherapy; no follow-up
[43]	2	Dumbbell	I:8 × 6 × 5	Few	Colon cancer	—	Alive at 13 y
[44]	2,3	Dumbbell	NS	Well diff	Benign uterine tumor	—	Preoperative chemotherapy and radiotherapy, postoperative chemotherapy; died at 54 mo with lung metastases
[45]	3	Intr.	7.5 × 7 × 4	Minimal	Goitre	—	NED at 13 mo
[46]	2	Dumbbell	16 × 10 × 9	—	—	Liver metastases	Alive at 23 mo
[47]	3	Dumbbell	4 × 3.7 × 3	5/hpf	—	—	No follow-up
[48]	2	Dumbbell	NS	High	Uterine lesion, NS	Tumor thrombus to HV	Postoperative chemotherapy; NED at 5 mo
[52]	2	Extr.	15	—	—	Duodenum invaded, liver metastases	Liver metastases at 16 mo, resected; skin metastases at 28 mo, immunotherapy; died at 79 mo.
[56]	2,3	Extr.	Large	Frequent	—	—	Lung and bone metastases at 2 y; died at 3 y.
[58]	3	Extr	6 × 3 × 6	—	—	—	Postoperative radiotherapy; local recurrence at 16 mo, resected; at 29 mo, resected + radiotherapy; died at 36 mo
[61]	2,3	Intr	—	Mod diff	—	Liver, kidney, gall bladder metastases	NED at 20 mo.
[62]	3	Extr	10 × 10	—	—	—	Lost to follow-up (+)
[62]	3	Extr	Large	—	—	—	Lost to follow-up (+)
[63]	3	Extr	15 × 9 × 9	5–27/10 hpf	—	—	Local recurrence at 30 mo, resected; NED at 90 mo (+)
[64]	2	Extr	7 × 6	—	—	—	NED at 3 y
[65]	2	Dumbbell	NS	High	—	Tumor thrombus into HV	NED at 15 mo
[66]	2	Dumbbell	Large	Well diff	—	—	Partial resection + chemotherapy + radiotherapy; alive at 6 mo
[66]	2,3	Dumbbell	Large	Well diff	—	Omental deposit	Postoperative radiotherapy; liver metastases at 30 mo; died at 33 mo with local recurrence and liver metastases
[67]	2	Extr	10 × 7.5 × 5	Mod diff	—	—	Liver metastases at 6 mo; died at 16 mo (+)

Continued

TABLE II. Leiomyosarcoma of the Inferior Vena Cava, Resected Cases (N = 89): Pathologic Features, Treatment, and Outcome (Continued)

Ref	Level[a]	Growth pattern[b]	Size (cm)	Mitosis grade[c]	Associated pathology	Extent of tumor[d]	Further treatment/outcome[e]
[68]	2,3	Dumbbell	E:6 × 6.6 I: 15.2 × 3	—	—	Tumor thrombus into RA	Recurrent RA tumor thrombus + intra-abdominal + pericardial deposits at 7 mo, debulking; alive at 1 y
[69]	2	Extr	12	2	—	—	No follow-up
[70]	3	Dumbbell	9 × 9 × 5	Well diff	—	—	NED at 2 mo
[71]	3	Extr	NS	3–4 hpf	—	—	Died with liver metastases at 48 mo
[72]	2	Dumbbell	8 × 7 × 6	<3 hpf	—	—	Postoperative radiotherapy; NED at 2 y
[73]	2	Extr	Large	—	—	—	No follow-up
[73]	3	Extr	NS	—	—	—	No follow-up
[74]	3	Extr	15 × 6	—	—	—	Postoperative chemotherapy; alive at 8 mo
[75]	2	Dumbbell	23 × 13 × 9	6/10 hpf	—	—	No follow-up
[76]	3	Dumbbell	17 × 2	—	—	—	Postoperative radiotherapy; died at 4 y with widespread metastases
[76]	2,3	Extr	18 × 14	Rich	—	Tumor thrombus to HV	Postoperative radiotherapy; NED at 8 mo
[76]	2,3	Extr	19 × 12	—	—	—	Liver metastases; died at 16 mo
[77]	3	Dumbbell	Large	—	—	Tumor thrombus into HV	Partial resection + postoperative chemotherapy; died at 3 mo, Budd-Chiari syndrome
[77]	2	Extr	10	—	Uterine lesion, not specified	—	Postoperative radiotherapy; NED at 4 mo
[78]	3	Dumbbell	Large	—		Liver metastases	No follow-up
[79]	2	NS	15 × 10	—	—	—	Preoperative chemotherapy; NED at 11 mo
[81]	2,3	Dumbbell	Large	—	—	—	Bone metastases at 1 y, radiotherapy
[82]	2	Extr	20 × 13 × 10	—	—	—	No follow-up
[83]	2	Extr	10	Frequent	Uterine myoma	—	Died 20 days postoperatively, bleeding
[84]	3	Dumbbell	5	—	—	—	Died 2 weeks postoperatively, pneumonia
[88]	2	Extr	4 × 2.5 × 2	10 hpf	Uterine myoma	—	NED at 9 mo
[89]	2	Extr	14 × 10 × 10	Low	—	—	Died at 9 mo, cause unknown
[93]	2	NS	10	—	—	—	Alive at 3.5 y
[95]	3	NS	—	—	—	—	Died at 8 mo, widespread metastases
[*]	2	Extr	11 × 9 × 9	1–5 hpf	—	—	Died at 23 mo, postoperative pancreatitis, widespread metastases
[*]	3	Extr	11	I–II	—	—	Alive at 70 mo, NED
[*]	3	Extr	4.5 × 3.5	I	—	Widespread metastases	Alive at 15 mo

[a]1: IVC from HV to RA; 2: IVC from RV to HV; 3: IVC from RV to confluence of IVC; (!) = 5 tumors were Level 3, 2 were Level 2,3, and 1 was Level 2; (*) = our cases.
[b]Extr = extrinsic; Intr = intrinsic.
[c]hpf = high power field; diff = differentiated
[d]RA = right atrium; LN = lymph node; HV = hepatic vein;
[e]NED = no evidence of disease; (+) = personal communication.
NS = not specified.

Diagnostic Tests

Hematologic and chemistry profile were normal in most cases. Liver enzymes were elevated when the hepatic veins were involved by tumor or tumor thrombus. Albuminuria was similarly noted with tumors involving the hepatic or renal veins [2,3,19,23,31,56,57]. Polycythemia and microangiopathic anemia were also observed [2,3,28,48,58,59].

Gastrointestinal and intravenous contrast studies demonstrated an extrinsic mass effect. Hepatic and renal scintigraphy revealed localized decreased or increased uptake. These studies were utilized in earlier reports as hepatic or renal diseases were suspect. Such tests were nonspecific and did not give information about the origin of the tumor. Ultrasonography was used to rule out hepatobiliary and pancreatic pathology and to confirm the

presence of a tumor. The tumor appeared as a mass with homogenous or heterogenous sound patterns [5,26,28, 39,36,41,48,60–68]. Doppler ultrasound gave information about patency of the portal or systemic venous system [41,48,65].

Computerized tomography (CT scan) and nuclear magnetic resonance (NMR) confirmed the presence of a tumor, its pattern of growth, relationship to the surrounding structures, and the presence of caval obstruction. On CT scan, the tumor appeared as low density, solid, or heterogenous mass compressing or silhouetting, involving or arising from the IVC [5,24,26,29,34,38–41,48,60–63,65–75]. Mild to moderate contrast enhancement, especially peripherally between the intraluminal growth and the cava wall, was noted [26,38,60,62,73–75]. NMR gave similar information to CT scan, but the sagittal section was more informative as to the extent of the tumor and tumor thrombus [11,39,40,61,65,67,68]. Although on CT or NMR scan, the presence of intraluminal abnormal signal, low density mass, or filling defect were sensitive indicators for the presence of a thrombus, such findings were not specific for a tumor thrombus. Combined with percutaneous transvenous biopsy, the diagnosis LMS of the IVC was made in two cases [34,41].

On angiography, LMS of the IVC exhibited variable degrees of vascularity [14,15,24,26,29–31,36,38,44, 56,59,61–78]. Hypervascular tumors derived their blood supply from the hepatic artery or its branches, adrenal, lumbar, gastric, pancreaticoduodenal, or gastroduodenal artery. More consistent angiographic findings were distortion, displacement, stretching, as well as compression of major vessels particularly the IVC. Retroperitoneal sarcomas could not be differentiated from LMS of the IVC angiographically [14]. In addition to luminal occlusion and collateralization, venography and intravenous cardioangiography revealed distortion of cava wall, the presence of intraluminal caval or cardiac growth, or filling defects. These findings were reliable criteria for the diagnosis of the tumor and proved informative when operative venous reconstruction was entertained [11,34, 41,42].

Percutaneous needle biopsy allowed identification of the histologic subtype of the tumor but not the organ of origin [24,34,38,48,66,67,79].

Treatment

The treatment in one case (0.75%) was not specified [14]. The tumor was an incidental autopsy finding in three cases (2.3%) [6–8]. The tumor was not resected in 40 cases (30%) (Table I). Attempt at resection in one case resulted in severe hemorrhage and death, and a decompressive procedure, mesoatrial shunt with right atrium tumor thrombectomy, performed in another case resulted also in hemorrhagic shock and death [11,60]. In 13 cases (32.5%), a celiotomy without tumor resection was performed [17,21,23,31,32,36,38,57,59,77,80]. A celiotomy was not performed in 25 cases (62.5%). The tumor in the nonresected cases was suprarenal in origin (Level 1, or Level 1,2), or intrahepatic (Level 2, Level 3, or Level 2,3) and exhibiting an extensive proximally propagating tumor thrombus. The tumor or tumor thrombus occluded the IVC and hepatic veins, or entered the right side of the heart or its outflow tract. This resulted in liver cell necrosis, cardiac valvular or outflow obstruction, or pulmonary oligemia. As the tumor was not suspect in these cases, the diagnosis and surgical intervention were delayed and hence patients reached a moribund state. Furthermore, when discovered at surgery, the tumor was deemed unresectable. These patients succumbed to liver failure or cardiopulmonary decompensation as a result of the local effect of the primary tumor or the propagating thrombus. Even when resection was possible, early postoperative death was a certain outcome [12,60].

A total of 89 tumors (66.9%) were resected [Table II]. Complete excision with a tumor-free margin was the ideal and when not feasible, debulking offered good palliation. Partial excision was performed in six cases (6.7%). The extraluminal growth was amputated in two cases, and with additional therapy (radiation therapy, chemotherapy) survival ranging from 4–6 months was achieved [66,77]. The intraluminal growth was removed in one case and death from liver failure was avoided [41]. No further treatment was given in one case and the tumor was allowed to ''regrow'' only to be resected later with attainment of a 5-year survival [11]. Complete excision was accomplished in stages in two cases [24,52]. Almost-complete-resection (microscopic disease left behind) was performed in two cases (2.25%) [24,26].

A total of 83 tumors were completely resected (93.3%). Complete resection entailed excision of the tumor, a portion of the IVC, the intracaval extension, concomitant metastatic disease, and involved nearby structures. Resection of intrahepatic IVC tumors was performed utilizing standard vascular techniques, i.e., control of the IVC and its tributaries proximal and distal to the tumor. More recently, venovenous bypass and extracorporeal circulation techniques were used to resect pararenal tumors [39,61]. The extent of vein resection (tangential or segmental) depended on the patency of the IVC and degree of involvement by tumor. Patency of the IVC following tangential excision was maintained with lateral venorrhaphy or patch angioplasty [11,26]. Ligation of the IVC following segmental resection was commonly performed as the collateral channels that developed as a result of gradual occlusion of the cava allowed venous drainage. Graft replacement (autograft or synthetic) of intrahepatic IVC was performed in 11 cases [5,11,12,39,40,47,48,61,63,65,68]. The long-term patency rate of these grafts was not recorded in all cases,

and thrombosis occurred 3 months to a year after reconstruction in three of these cases [5,11,40]. The right kidney was often removed en bloc with the tumor when venectomy was deemed necessary. The right kidney was preserved, by pelvic transplantation, in one case only [77]. However, the left kidney was often preserved following venectomy or ligation of the renal vein. Collateral circulation via the adrenal, gonadal and lumbar branches allowed adequate venous drainage. Implantation of the left renal vein in the upper or lower IVC stump or in the graft was performed in seven cases [40,56,61,73,76,81]. Resection of concomitant metastatic disease was performed in six cases [37,46,52,61,66,78]. Resection of involved nearby structure (excluding the kidney) was performed in three cases [24,25,52]. Removal of associated limited-in-extent tumor thrombus was performed in three cases [37,48,76]. Removal of a more extensively propagating tumor thrombus was more demanding and required cardiopulmonary bypass with circulatory arrest, venovenous bypass and total hepatic vascular exclusion. The use of such techniques was further extended in recent years to facilitate resection and replacement of supra and retrohepatic IVC, disobliteration of occluded hepatic veins, and to perform extensive liver resection [39–41,48,60,65,68]. Right atrial tumor thrombus was removed in four cases. Early postoperative death from liver failure occurred in two cases [12]. The atrial thrombus recurred with intraabdominal and pericardial deposits at 7 months in one case, and with debulking the patient remained alive for 1 year [68]. Survival with no evidence of disease for 12 months was achieved in the fourth case [40]. Hepatic vein tumor thrombectomy performed in one case was associated with a survival of 15 months [65].

The most common intraoperative complication following almost-complete and complete resection was hemorrhage, which occurred in three cases (3.5%) [18,44,82]. The postoperative morbidity was 15%, the most common being phlebitis [15,18,24,35,37,39,47,52,65,82–84]. Death in the postoperative period occurred in five cases (6%) [11,12,83,84]. Adjuvant therapy was administered in 21 almost-completely and completely resected cases. The impact of such modality of therapy could not be ascertained given the small number of cases treated and the variability of the agents used, their dose and duration of administration, as well as patient selection. The theoretical benefits of adjuvant therapy would be to downstage the tumor, eliminate micrometastasis and prevent progression, or delay recurrence. Given preoperatively, good response allowed resection in three cases [24,26,79]. Given postoperatively, such treatment failed to impact significantly on outcome of resection [11,12,26]. Despite the unproven benefit, given the poor prognosis of the tumor, and since the overall objective response rate to recent sarcoma protocols approached 50%, neoadjuvant therapy would be indicated in high risk LMSs [85]. Moreover, in situ response of the tumor to neoadjuvant therapy could be used to determine if continuation of therapy postoperatively would be appropriate [86].

Recurrent disease following almost-complete and complete resection was treated with resection, chemotherapy, radiation therapy, or a combination. Surgical excision of solitary metastasis or dubulking of intraabdominal recurrence offered good palliation and achieved survival ranging from 12 to 90 months [10,11,24,25,52,58,63].

Biologic Behavior

LMS of the IVC was considered a slowly growing tumor. In three cases a rather rapid growth rate was evident [15,31,71]. In these cases the tumor was reported to be not present on previous laparotomy performed 6–24 months for unrelated disorders. The tumor metastasized late in the course of the disease. The tumor spread mainly systemically and most commonly to the liver and lungs, but no organ was exempt. Lymph node metastasis occurred less frequently as it occurred in five cases only including our case [13,21,41,42]. Metastatic disease was initially present in 8 of 89 resected cases (8.9%), in 13 of the 40 nonresected cases (32.5%), and in none of cases where the tumor was an incidental autopsy finding. Recurrent disease developed in the two almost-completely-resected tumors, local in one case and systemic in the second [24,26]. Recurrent disease following complete tumor resection developed in 30 of 78 patients who survived the surgery (38.5%). Local-only-recurrence developed in three cases (10%), systemic in 24 cases (80%), and intracavitary in two cases (6.7%). Local recurrence was present in addition to systemic or intracavitary recurrence in three cases including one of our cases [66,68]. These recurrences developed 6 months to 5 years following resection, but the great majority occurred within 30 months.

We examined several clinicopathologic variables to determine the ones important in determining resectability and prognosis of the tumor. Unfortunately, histopathologic data and follow-up information were not available in all patients making meaningful comparison at times difficult to ascertain.

Level of origin of the tumor, pattern of growth, and the extent of the intracaval growth were important prognostic factors. Suprarenal tumors (Level 1 and Level 1,2) were nonresectable and uniformly fatal and early postoperative death occurred when such tumors were resected or bypassed [12,60]. At that location the tumor interfered with the circulation to the liver and the in-flow to the right side of the heart, thus resulting in liver cell death, cardiac valvular, and outflow tract obstruction. Such tumors behaved in a malignant fashion by virtue of their location. Intrahepatic LMS behaved in a similar

fashion when the intrinsic growth extended intraluminally as a tumor thrombus especially when coupled with delayed diagnosis and intervention. In five of the completely resected tumors, tumor thrombus was removed from the right atrium (RA) in four cases and from the hepatic veins in one case. Early postoperative death from liver failure occurred in two cases, recurrent RA tumor thrombus in one case, and survival with no evidence of disease for 12–15 months occurred in two cases [12,40,65,68].

However, Level 2, Level 2,3, and Level 3 tumors exhibiting an extrinsic or bidirectional growth with a limited intracaval extension were resectable, and prolonged survival was possible. We examined the prognostic significance of encapsulation, presence of tumor necrosis, size of the tumor, level of origin, extent of caval resection, and histologic appearance of the tumor. The presence of a capsule was not a sign of benignity. However, once breached (spontaneously or iatrogenically, i.e., at initial partial resection), recurrence was common. Recurrence developed in the six cases where the capsule was breached [16,24–26,52]. Tumor necrosis and size did not reflect the biologic behavior of the tumor. Level 2 tumors appeared to have more prolonged survival compared to Level 3 tumors. Of patients with Level 2 tumor (17/25 cases where follow-up period was specified), 68% were alive with no evidence of disease for 4–156 months. Yet, 50% of patients with Level 3 tumors (12/24 cases) were alive with no evidence of disease for 3–78 months following complete resection.

Radical excision of the IVC, i.e., segmental excision compared to cuff excision, did not have an impact on the outcome of the resection. Of the cases where segmental resection of the IVC was performed, 32 patients survived the operation and were available for follow-up. Local recurrence developed in three of these cases (9.4%) [58,63,68]. Systemic recurrence developed in 12 cases (37.5%) [9–12,24–26,52,56,76,81]. Survival with no evidence of disease for 3–78 months was observed in 17 cases (53%) [5,26,35,39,40,44,45,48,61,65,70–72,74,76,77,79]. In cases where cuff excision of the IVC was performed, 21 patients (including our cases) survived the operation and were available for follow-up. Local recurrence developed in two cases (9.5%) and systemic in three cases (14.3%) [11,16,67]. Survival with no evidence of disease for 2 months to years after resection was noted in 16 cases (76.2%) [11,15,18,22,24,26, 37,39,43,46,64,88]. In the 13 cases of LMS of the IVC reported by Burke and Virmanti [12], the tumor was ''removed with a portion of the IVC'' in 12 cases, and none recurred locally.

Furthermore, prognosis following complete resection varied according to the histologic features of the primary tumor. Although such data was available in 46 cases, follow-up period was specified in only 33 cases. The tumor was well differentiated, Grade I, with minimal, few, or less than five mitotic figures/hpf, in 14 cases. Synchronous metastatic disease was present in one case (our case), and metachronous disease developed in four cases (28.6%). Survival with no evidence of disease for 3 months to 13 years was noted in nine cases (64.3%). The tumor was moderately differentiated or grade 2 in five cases. Survival with no evidence of disease for 9 months to years was observed in three cases (60%), local recurrence developed in one case (20%) (the capsule was microscopically breached), and systemic spread in one (20%). The tumor was poorly differentiated, grade 3, with frequent or more than 10 mitotic figures/hpf in 14 cases. Survival with no evidence of disease occurred for 2–15 months in eight cases (57%), whereas systemic spread occurred 3 months to 2 years in six cases (43%). Overall distant recurrence developed in 6/19 (31%) patients with Grade I or II tumors and in 6/14 (43%) of Grade III tumors. However, Dzsinich et al. [11] did not find a correlation between mitotic activity and clinical outcome in their 13 cases of primary LMS of the vein.

Given the relatively small number of patients with LMS of the IVC having documented grade and follow-up, and the variation of other important prognostic indicators, such as stage, anatomic location, extent and size of the primary tumor within each grade, the evidence from this review on the prognostic importance of grade for this tumor is not definitive. However, considering the powerful prognostic significance of grade in soft tissue sarcomas in general or leiomyosarcomas of all anatomic locations, there is no reason to doubt its potential prognostic value in LMS of the IVC.

CONCLUSIONS

LMS of the IVC is a rare tumor that commonly affects females. In this review, the clinical manifestations were diverse and nonspecific. In the absence of specific signs and reliable markers, a high index of suspicion and utilization of CT scan allow early recognition. NMR and transvenous biopsy allow accurate diagnosis, staging, and delineation of the extent of the tumor.

The tumor originated from the lower two-thirds of the IVC in two-thirds of the cases and exhibited an extrinsic growth in >50% of the cases. The tumor often grew slowly, assumed a large size without direct infiltration of nearby structures, and spread systemically late in the course of the disease. The tumor behaved in a malignant fashion by virtue of its location and extent of intracaval growth. Tumors arising from Level 3 of the IVC, incomplete excision, presence of capsular invasion, and higher grade, portended poor prognosis.

Surgical resection of the tumor with a free margin was the only therapeutic modality associated with prolonged survival. Resection of tumors in the area of the hepatic veins required extracorporeal techniques. Similarly, re-

section of intrahepatic tumors exhibiting an extensive proximally propagating tumor thrombus required such approach. Although long-term outcome was not satisfactory in such cases, it was the only means of palliation. Intrahepatic tumors exhibiting an extraluminal growth or intraluminal growth limited in extent were more amenable to resection using standard vascular techniques. Reconstruction of the IVC was not always required in these cases. When complete resection was deemed not possible, debulking combined with radiation therapy provided good palliation. Tumor thrombectomy alone prevented death from liver failure and right heart outflow tract obstruction in some cases. The role of neoadjuvant therapy is not clear; it may be given preoperatively to downsize the tumor and increase resectability rate. In the postoperative period adjuvant therapy may be indicated in high risk tumors.

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